REMARKS

Claims 2, 3, 5, and 7-14 are pending in the application. Claims 9-14 have been cancelled by this amendment. Therefore, claims 2, 3, 5, 7, and 8 are at issue.

This amendment is submitted in accordance with 37 C.F.R. §1.116(a) and §1.116(b) in order to present the rejected claims in a better form for allowance or appeal. The amendment is necessary to eliminate rejections under 35 U.S.C. §102 and 35 U.S.C. §103. This amendment was not presented earlier because the rejections under 35 U.S.C. §102 and 35 U.S.C. §103 are new grounds of rejection. The amendment should be entered because it places the application in better form for allowance or appeal, and the amendment does not require further searching or present any new issues.

In this amendment, claims 9-14 have been cancelled, and the features of claims 9-13 have been incorporated into claim 5. Claim 5 now recites various neuropathies treated by the present method. For the reasons set forth below, it is submitted that the present claims are patentable over the cited references, and that the application should pass to issue.

Claims 2, 3, 5, 7, 8, 11, and 14 stand rejected under 35 U.S.C. §102(e) as being anticipated by Laties et al. U.S. Patent Publication No. 2002/011997 ('997). In view of the amendments to the claims, and for the reasons set forth below, it is submitted that this rejection is in error and should be withdrawn.

First, the rejection of claim 14 is moot in view of the cancellation of claim 14. Therefore, the sole issue in this rejection is the subject matter of claim 11, which now is recited in claim 5. The examiner contends that macular degeneration is a degenerative neuropathy. However, this contention is not correct.

The '974 publication teaches a method for treating macular degeneration, but does *not* teach that macular degeneration is a degenerative neuropathy. For example, in the Summary of the Invention, at paragraph [0011], the '974 publication states:

> "[0011] This invention is directed to novel methods and compositions for treating and preventing acute, sub-acute, and chronic diseases and conditions of the eye. Examples of acute, sub-acute, and chronic diseases and conditions of the eye include, but are not limited to: central retinal or posterior ciliary artery occlusion; central retinal vein occlusion; optic neuropathy including, but not limited to, anterior ischemic optic neuropathy and glucomatous optic neuropathy; and macular (dry) degeneration."

It is notable that this paragraph recites diseases and conditions of the eye and *separates* optic neuropathies from macular degeneration by a semicolon. Furthermore, paragraphs [0015] and [0017] of the '974 publication teach that optic neuropathies are the third embodiment of the invention, but macular degeneration again is separated from optic neuropathies in paragraph [0018] as the fourth embodiment of the invention. The '974

publication is silent with respect to identifying macular degeneration as a degenerative neuropathy.

Accordingly, the examiner's contention that macular degeneration is a degenerative neuropathy is an unsupported assertion. It is submitted that because a condition contains the term "degeneration" in its name, does not automatically make that condition a degenerative neuropathy.

In addition, applicants include various pages from Dorland's Illustrated Medical Dictionary, 29th Edition (2000) as Exhibit A. In page 1212, a neuropathy is defined as a disturbance or change in the *peripheral* nervous system. However, macular degeneration is not a condition of the peripheral nervous system, but of the *central* nervous system. The examiner's attention is directed to U.S. Patent No. 5,527,533, submitted concurrently with this amendment as Exhibit B. In particular, the examiner is directed to column 1, lines 7-36 of Exhibit B, wherein it is explained that retinal conditions, like macular degeneration, are *central* nervous system disorders. Especially note column 1, lines 28-32. The eye includes the *optic nerve*, which is part of the central nervous system, and is different from a peripheral nerve. The examiner is further directed to Exhibit C submitted concurrently with the amendment. Exhibit C is the first page of a 1992 publication specifically stating that the retina is an integral part of the central nervous system. Also, see Exhibit A, p. 239, showing that the optic nerve is a part of the central nervous system, and p. 466, wherein the definitions of macular

degeneration do not implicate the peripheral nervous system.

In summary, in view of the amendments to the claims, and for the reasons set forth above, it is submitted that the rejection of claims 2, 3, 5, 7, and 8 as being anticipated by the '974 publication should be withdrawn. It is further submitted that the pending claims would not have been obvious over the '974 publication because the cited reference is limited to treating diseases of the eye, and fails to teach or suggest treatment of the presently claimed neuropathies.

Claims 2, 3, 5, 7, 8, and 11 stand rejected under 35 U.S.C. §102(b) as being anticipated by a Brewer et al. publication (Brewer) evidence by Dorland's Illustrated Medical Dictionary (Dorland's). First, applicants question the propriety of this rejection under 35 U.S.C. §102(b) because the examiner is relying on a secondary reference to add to the disclosure of the primary reference. Regardless of this apparent error, the present claims are neither anticipated by, nor obvious over, Brewer alone, or Brewer in combination with Dorland's.

The examiner contends that the present claims are anticipated because Brewer teaches the treatment of erectile dysfunction (ED) in patients suffering from Parkinson's disease (PD), and because Dorland's states that autonomic neuropathy has a symptom that includes sexual functions. The examiner is clearly relying on Dorland's to add to the disclosure of Brewer, and the rejection, therefore, is improper.

Although this rejection is improper, the present claims are patentable over the cited references, either Brewer alone or a combination of Brewer and Dorland's. In particular, Brewer teaches no more than the treatment of ED in men suffering from PD. The reference teaches the use of a commercially available treatment for ED (i.e., sildenafil) in patients with "probable" PD-related impotence. Brewer found that sildenafil was effective with side effects like those found in healthy males that use sildenafil.

The reference is silent with respect to treating the parasympathetic nervous system diminution that *may* lead to ED in PD sufferers. Brewer did not attempt to treat any neuropathies, nor does the cited reference suggest that the therapy could treat a neuropathy. Brewer merely teaches treatment of a symptom of a neuropathy. The Dorland's reference fails to cure the deficiencies of Brewer.

Dorland's teaches that an autonomous neuropathy can have sexual function symptoms, however, several diseases have sexual function symptoms. In contrast to the examiner's statement, Dorland's does not "show the Parkinson's diseas [sic] is a degenerative disease of autonomic neuropathy." Dorland's is *silent* with respect to any teaching or suggestion that PD is a neuropathic disease. The examiner's attention is directed to pages 1317 of Exhibit A, wherein the definition of Parkinson's disease is of unknown etiology. Also, see U.S. Patent No. 5,753,225, cited by the examiner in this Office Action, which teaches

that PD is a central nervous system disorder (column 2, lines 7-20).

In summary, it is submitted that Brewer, alone or in combination with Dorland's, fails to anticipate the present claims or render the present claims obvious. Brewer's teachings are limited to treating ED in males suffering from PD. The reference is *silent* with respect to treating a neuropathy, and provides no motivation or incentive for a person skilled in the art to use sildenafil to treat a *neuropathy*, as presently recited in claim 5. A skilled person would read no more into the Brewer reference than a successful treatment of ED, using a known, commercial compound for treating ED, in a subset of males who suffer from PD and have ED as a symptom. Dorland's does *not* teach or suggest the PD is a degenerative disease of autonomic neuropathy. Dorland's merely states that sexual function is one possible symptom of an autonomic neuropathy. Brewer teaches treating of this symptom, i.e., ED, but not the underlying neuropathy. Accordingly, it is submitted that this rejection of claims 2, 3, 5, 7, and 8 (claim 11 has been incorporated into claim 5) is in error and should be withdrawn.

Claims 2, 3, 5, 9, 12, and 13 stand rejected under 35 U.S.C. §103 as being obvious over DuBois U.S. Patent No. 6,399,601 ('601) in view of U.S. Patent No. 5,972,342 ('342) and further in view of U.S. Patent No. 5,753,225 ('225). The rejection is based on a contention that DuBois '601 teaches a composition containing sildenafil for treating diabetes and diabetic compli-

cations. For the reasons set forth below, it is submitted that this rejection is in error and should be withdrawn.

First, the examiner mischaracterizes the '601 patent. The '601 patent is directed to compounds of Formula I that (a) *differ substantially* from sildenafil and (b) are useful in the treatment of diabetes *and* in the treatment of diabetic complications ('601 patent, column 23, line 63 through column 24, line 2). The '601 patent goes on to state that a litany of other drugs having several different modes of action can be used in conjunction with the compounds of Formula I to *treat* diabetes (column 24, line 18). This long list includes sildenafil as an agent to *treat* diabetes. More particularly, the '601 patent states:

> "Diabetes can be treated by administering to a patient having diabetes (Type I or Type II), insulin resistance, impaired glucose tolerance, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or cataracts, *a therapeutically effective amount of a compound of the present invention.* It is also contemplated *that diabetes be treated* by administering a compound of the present invention or an other [sic] glycogen phosphorylase inhibitors that are useful in combination with other agents useful to treat diabetes and/or obesity include those of Formula I. Additional preferred glycogen phosphorylase inhibitors are disclosed in PCT publications WO 96/39384 and WO 96/39385." (column 24, lines 3-17, emphasis added).

The '601 patent clearly states that a compound of Formula I (different from sildenafil) treats diabetes *and* diabetic complications. The '601 patent then goes on to state that other agents can be used with a compound of Formula I to treat *diabetes*. These other agents are not taught as being capable of treating diabetic complications.

As stated above, the '601 patent lists compounds and class of compounds that purportedly treat diabetes at column 24, lines 18-67. This list contains no less than *thirty* classes of compounds, and a multitude of individual compounds, that act by inhibiting vastly different enzymes or by other unrelated biological processes. *No* differentiation is made with respect to which compounds treat diabetes or which compounds treat obesity.

Furthermore, the '601 patent *requires* that compound of Formula I be present in the composition to treat diabetes complications. Applicants have found that the neuropathies recited in claim 5 can be treated by the compounds recited in claim 5 alone, without requiring the presence of a compound of Formula I. This is a new and unexpected finding in view of the '601 patent that specially *requires* the presence of a compound of Formula I.

In summary, the '601 patent fails to teach or suggest that sildenafil can be used alone, without a compound of Formula I of the '601 patent, to treat diabetes. In fact, throughout the '601 patent, it is taught that a compound of Formula I is necessary for the treatment. Notably, the '601 patent teaches that

sildenafil treats diabetes, or obesity but is silent with respect to sildenafil treating diabetic complications.

In particular, the '601 patent at column 23, lines 63 through column 24, line 17 states that a compound of Formula I can treat diabetes *and* complications of diabetes. The '601 patent also states that a compound of Formula I can be used with a second agent useful in the treatment of diabetes or obesity (column 24, lines 8-12). Sildenafil is *not* taught in the '601 patent as a drug to treat complications of diabetes, but to actually treat the *diabetes or obesity* (see column 24, lines 18-19 and 38).

In contrast to the '601 patent, the present method utilizes sildenafil to treat neuropathies, *not* to treat diabetes. Note in Examples 1 and 2 of the specification that the patients were administered sildenafil to achieve an improvement of symptomatic pain and the symptoms and complications from diabetes, but *not* the disease itself.

The secondary and tertiary references do not overcome the deficiencies of the '601 patent. The '342 patent is directed to grain-derived mixtures and use of the same as medicaments. The '342 patent fails to add to the '601 patent, and fails to suggest that sildenafil can treat diabetic neuropathies. The portion of the '342 patent relied upon by the examiner merely is a list of diabetic complications and a list of other disease conditions purportedly treated by the disclosed grain-derived mixtures. The mixtures of the '342 patent are not related to sildenafil in general, or to

phosphodiesterase inhibitors in general, thus there is no motivation to combine the teachings of the '601 patent and the '342 patent and arrive at the presently claimed invention.

The tertiary '225 patent is directed to antibodies that mimic neurotrophins. The '225 patent is relied upon by the examiner for teaching the etiologies of a peripheral neuropathy. But the '225 patent, like the '342 patent, absolutely fails to teach or suggest that a phosphodiesterase inhibitor can be used to treat neuropathies. Applicants fail to find any disclosure in the '225 patent, or the '342 patent, that adds to the teachings of the '601 patent, such that a person skilled in the art would have been motivated to treat a neuropathy (as opposed to diabetes) using a compound presently claimed in claim 5 alone (as compared to using a claimed compounds in combination with a compound of Formula I of the '601 patent). Although the '342 and '225 patents teach neuropathies and the etiology of neuropathies, these references with the '601 reference fail to teach treatment of a diabetic neuropathy, a toxic neuropathy, or a metabolic neuropathy with a compound recited in the present claim 5.

For all the reasons set forth above, it is submitted that a person skilled in the art, after considering the combined teachings of the '601, '342, and '225 patents would have had no incentive to consider using a compound presently claimed in claim 5 to treat a *neuropathy*. Accordingly, the rejection of claims 1, 3, 5, 7, and 8 as being obvious over the cited '601, '342, and '225 patent should be withdrawn.

Claim 10 stands rejected as being obvious over the '601 patent in view of a Gentile publication. Applicants are confused with respect to this rejection because at page 2 of the Office Action, the examiner has *expressly* withdrawn the rejection of the subject matter of claim 10 under 35 U.S.C. §103 based on a combination of the '601 patent and the Gentile publication. In view of the conflicting nature of the Office Action, applicants request the reissuance of a clear Office Action, as required under 37 C.F.R. §1.104(c). However, if the rejection of claim 10 has indeed been overcome, a reissuance of the Office Action is obviated.

To assist the examiner, applicants incorporate by reference the patentability arguments provided in Amendment "B" filed July 14, 2004. In addition, the '601 patent and the deficiencies of the '601 patent have been discussed above. The Gentile publication fails to cure the deficiencies of the '601 patent. The Gentile publication merely states that autonomic diabetic neuropathy of the alimentary canal takes several forms, and that diabetics should be aware of bile disorders. The Gentile publication is totally silent with respect to using sildenafil to treat a neuropathy.

In summary, a person skilled in the art, after reading the '601 patent and the Gentile publication, in combination, would not have considered administering sildenafil in a method of treating a neuropathy as recited in claim 5. The references, alone or in combination, fail to provide any motivation for a

person skilled in the art to consider using sildenafil in the claimed amounts to treat a *neuropathy*. Therefore, as recognized in the Office Action, the subject matter of claim 10, now incorporated into claim 5, is patentable over the '601 patent in view of the Gentile publication.

In summary, it is submitted that all pending claims are in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

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Exhibit A

29th EDITION

DORLAND'S Illustrated MEDICAL DICTIONARY

W.B. SAUNDERS COMPANY
A Harcourt Health Sciences Company
Philadelphia London Toronto Montreal Sydney Tokyo

W.B. SAUNDERS COMPANY
A Harcourt Health Sciences Company

The Curtis Center
Independence Square West
Philadelphia, PA 19106

Dorland's illustrated medical dictionary.
Philadelphia: W.B. Saunders Co.,
v.: ill.; 27 cm.
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Began publication with 23rd ed.
Description based on: 26th ed.
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[DNLM: 1. Dictionaries, Medical. 2. Reference Books, Medical]

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Indonesian *(26th Edition)*—E.G.C. Medical Publishers, Jakarta, Indonesia

Italian *(28th Edition)*—Edizioni Scientifiche Internazionali (ESI), Milan, Italy

Japanese *(28th Edition)*—Hirokawa Publishing Company, Tokyo, Japan

Portuguese *(28th Edition)*—Editiora Manole Ltda., São Paulo, Brazil

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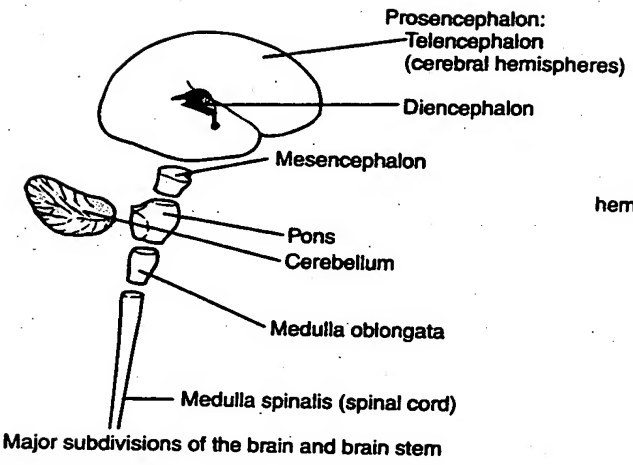
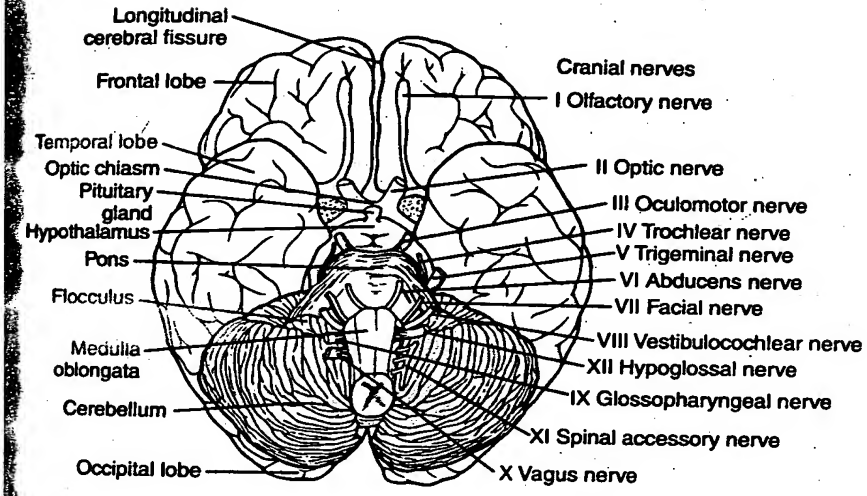
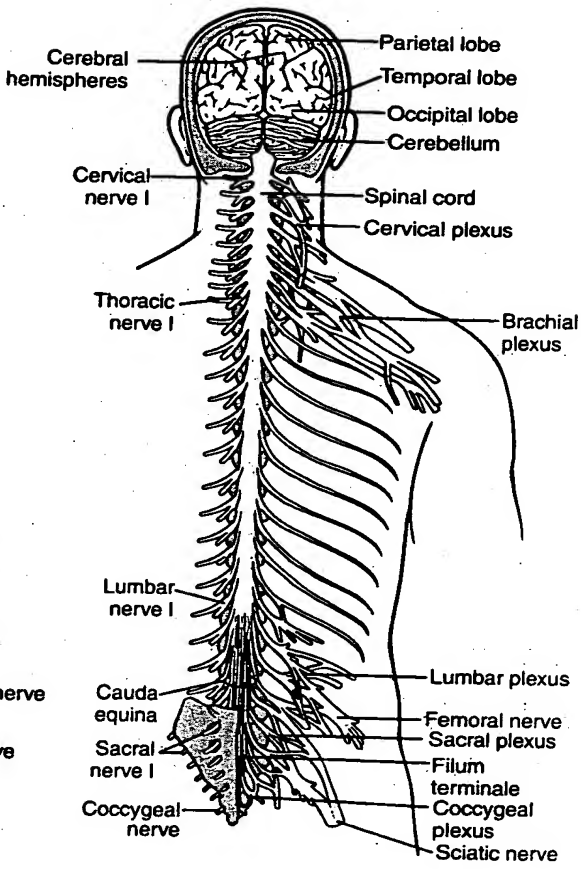


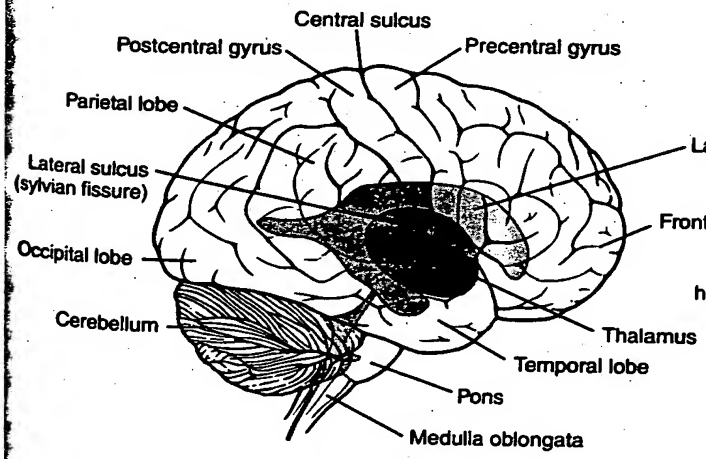
Major subdivisions of the brain and brain stem



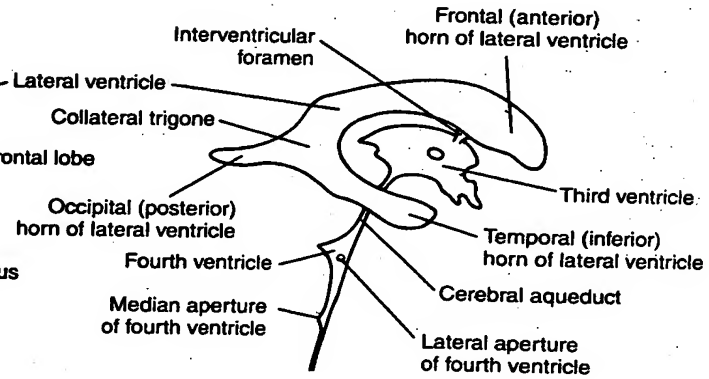
Basal view showing the brain stem and cranial nerves



Posterior view showing the dorsal *(left)* and ventral *(right)* rami of the spinal nerves



Lateral view showing cortical lobes



Lateral view of ventricles

PLATE 11—VARIOUS ASPECTS OF BRAIN AND SPINAL CORD

adipose d., fatty d.
adiposogenital d., adiposogenital dystrophy.
Alzheimer's neurofibrillary d., neurofibrillary tangles.
angiolithic d., one characterized by mineral deposits and hyaline changes in the coats of the vessels.
Armanni-Ebstein d., see under *lesion*.
ascending d., wallerian degeneration affecting centripetal nerve fibers and progressing toward the brain or spinal cord.
atheromatous d., atheroma.
atrophic pulp d., pulp atrophy.
axonal d., 1. axonal reaction. 2. wallerian d.
ballooning d., hydropic d.
blastophthoric d., blastophthoria.
calcareous d., degeneration with infiltration of calcareous materials into the tissues; called also *earthy d.*
caseous d., caseation, def. 2.
cerebellar d., paraneoplastic, cerebellar d., paraneoplastic subacute, the most common paraneoplastic syndrome affecting the brain, occurring most commonly with ovarian and breast carcinoma and Hodgkin's disease, characterized pathologically by severe loss of Purkinje cells and clinically by insidious and progressive truncal and appendicular ataxia, dysarthria, nystagmus, and occasionally dementia. In some women with gynecologic or breast carcinoma, it is associated with an autoantibody (anti-Yo).
cerebellar d., primary progressive, a familial disease marked by motor disorders and due to cerebellar degeneration, occurring in adults between the ages of thirty and forty and progressing slowly to a fatal termination; called also *Holmes' d.*
cerebromacular d. (CMD), cerebroretinal d., 1. degeneration of brain cells and the macula luteae, as in Tay-Sachs disease. 2. any lipidosis with cerebral lesions and degeneration of the retinal macula. 3. any form of neuronal ceroid-lipofuscinosis.
cheesy d., caseation, def. 2.
colloid d., the assumption by the tissues of a gumlike or gelatinous character; called also *gelatiniform d.*
colloid d. of choroid, Tay's choroiditis.
comma d., progressive degeneration of the nervous matter of the comma tract (interfascicular fasciculus).
corticostriatal-spinal d., Creutzfeldt-Jakob disease.
Crooke's hyaline d., Crooke's hyalinization.
cystic d., degeneration with the formation of cysts.
cystoid d., Blessig's cysts.
descending d., wallerian degeneration extending peripherally along nerve fibers.
Doyne's familial colloid d., Doyne's honeycomb d., see under *choroiditis*.
dystrophic d., degeneration arising from defective or faulty nutrition.
earthy d., calcareous d.
elastoid d., amyloid degeneration of the elastic tissue of arteries.
familial colloid d., Doyne's familial honeycombed choroiditis.
fascicular d., degeneration of paralyzed muscles due to lesion in the motor ganglion cells of the central tube of gray matter of the cord.
fatty d., deposit of fat globules in a tissue; an older term for a concept now included in *fatty change*.
fibrinous d., necrosis with deposit of fibrin within the cells of the tissue.
fibroid d., degeneration of a leiomyoma with subsequent fibrosis.
fibrous d., fibrosis.
gelatiniform d., colloid d.
glassy d., a peculiar change occurring in the heart muscle and other muscles in fevers.
glistening d., degeneration of glia tissue characterized by the formation of glistening masses; called also *degeneratio micans* and *Rosenthal's d.*
glycogenic d., a form of degeneration in which abnormal amounts of glycogen accumulate in the cells, as in glycogenosis.
Gombault's d., progressive hypertrophic neuropathy.
granulovascular d., a condition in which the ganglion cells become filled with vacuoles containing condensed granules of protoplasm.
gray d., degeneration of the white substance of the spinal cord, in which it loses myelin and assumes a gray color.
hepatolenticular d., Wilson's disease.
Holmes' d., primary progressive cerebellar d.
Horn's d., degeneration with nuclear proliferation in striated muscles.
hyaline d., a regressive cellular change in which the cytoplasm takes on a homogeneous glassy eosinophilic appearance. Also used loosely to describe the histologic appearance of tissues. Called also *vitreous d.* and *hyalinosis*.
hydropic d., the swelling of cells caused by the accumulation of intracellular water in response to cell injury; called also *ballooning d.*
lattice d. of retina, a frequently bilateral, usually benign asymptomatic condition, characterized by patches of fine gray or white lines that intersect at irregular intervals in the peripheral retina, usually associated with numerous, round, punched-out areas of retinal thinning or retinal holes.
lipoidal d., a condition somewhat resembling fatty change but in which the extraneous material is lipoid.
macular d., degenerative changes in the macula retinae.
macular d., congenital, an autosomal dominant form of macular degeneration characterized by the presence of a cystlike lesion in the early stages resembles egg yolk; called also *vitelliform* or *vitelline macular d., Best's disease, Best's macular dystrophy,* and *hereditary vitelliform dystrophy.*
macular d., disciform, a form of macular degeneration occurring in persons over 40 years of age, in which sclerosis involving the macula and retina is produced by hemorrhages between Bruch's membrane and the pigment epithelium; called also *macular disciform d., senile exudative macular d., senile macular exudative choroiditis, senile disciform d., Kuhnt-Junius disease, disciform retinitis,* and *central disk-shaped retinopathy.*
macular d., senile exudative, disciform macular d.
macular d., Stargardt's, Stargardt's disease.
macular d., vitelliform, macular d., vitelline, congenital macular d.
macular disciform d., disciform macular d.
Mönckeberg's d., see under *arteriosclerosis*.
mucinoid d., a term used to include both mucoid and colloid degeneration; called also *mucinous d.* and *myelinic d.*
mucinous d., mucous d.
mucoid d., degeneration accompanied by deposition of myelin and lecithin in the cells.
mucous d., a form in which mucus accumulates in epithelial tissues.
myelinic d., mucoid d.
myofibrillar d., contraction band necrosis.
myxomatous d., degeneration in which mucus accumulates in connective tissues.
Nissl d., axonal reaction.
olivopontocerebellar d., see under *atrophy*.
pallidal d., degeneration of the globus pallidus, as in juvenile paralysis agitans.
pigmental d., pigmentary d., that in which cells of affected tissues become abnormally pigmented.
red d., degeneration of a uterine leiomyoma during pregnancy marked by the formation of soft red areas due to necrosis and edema.
retrograde d., axonal reaction.
rim d., degeneration of the spinal cord affecting the periphery only.
Rosenthal's d., glistening d.
sclerotic d., a variety of hyaline degeneration affecting connective tissue, especially the intima of arteries.
secondary d., wallerian d.
senile d., the widespread degenerative changes, principally fibroid and atheromatous, that occur in old age. Cf. *senile atrophy*.
senile disciform d., disciform macular d.
spongy d. of central nervous system, spongy d. of white matter, a rare, autosomal recessive form of leukodystrophy, characterized by early onset, widespread demyelination and vacuolation of the cerebral white matter that gives rise to a spongy appearance, severe mental retardation, megalocephaly, atony of the neck muscles, spasticity of the arms and legs, and blindness, with death usually occurring at about 18 months of age. Called also *Canavan's disease* and *Canavan-van Bogaert-Bertrand disease*.
striatonigral d., a form of multiple system atrophy in which nerve cell degeneration occurs mainly in the region of the substantia nigra and the neostriatum. Symptoms are similar to those of parkinsonism with rigidity, slowing of movements, poor balance, and mumbling speech, but parkinsonian tremor is absent.
subacute combined d. of spinal cord, degeneration of both the posterior and lateral columns of the spinal cord caused by vitamin B12 deficiency; a progressive disease, most often affecting persons over forty years of age, it is usually associated with pernicious anemia. The symptoms include paresthesias, ataxia, unsteadiness of gait, and sometimes emotional disorders. Called also *combined system disease, combined sclerosis, Lichtheim's disease* or *syndrome, Putnam-Dana syndrome,* and *posterolateral sclerosis*.
tapetoretinal d., degeneration of the pigmented layer of the retina as occurs in retinitis pigmentosa and other disorders.
transneuronal d., atrophy of certain neurons after interruption of afferent axons or death of other neurons to which they send their efferent output.
traumatic d., degeneration of a divided nerve up to the nearest node of Ranvier.
Türck's d., secondary parenchymatous degeneration of nerve tracts of the cord.
uratic d., degeneration marked by the deposit of urates or uric acid.
vacuolar d., the formation of vacuoles in the cells of a tissue.
vitelliform d. of Best, congenital macular d.
vitreous d., hyaline d.

pathway, beginning at the receptor and ending at a synapse with a secondary sensory neuron, often within a nucleus of the central nervous system. One common type is the pseudounipolar neuron.
projection n., one which serves for the transmission of nervous impulses, whether motor or sensory, between the cerebral cortex and other parts of the nervous system. See also *projection fibers*, under *fiber*.
pseudounipolar n., a unipolar neuron, almost always a primary sensory neuron, that was originally bipolar but whose two processes fused during development to form a single process that bifurcates at a distance from the cell body. One branch is structurally an axon with a myelin sheath but functions as a dendrite, with afferent conduction originating in a nerve ending.
Purkinje n's, see under *cell*.
pyramidal n., see under *cell*.
secondary sensory n., a sensory neuron that is the second in an afferent pathway, being stimulated at a synapse by a primary sensory neuron and often extending some distance into the central nervous system.
sensory n., any neuron with a sensory function; an afferent neuron conveying sensory impulses. Cf. *primary sensory n.* and *secondary sensory n.* See illustration accompanying *nerve*.
spiny n., a neuron whose dendrites have many spines (gemmules), such as a Golgi type I neuron.
unipolar n., a neuron with one process only; see also *pseudounipolar n.*

neu·ro·nal (noor'o-nəl) pertaining to a neuron or neurons.

neu·rone (noor'ōn) neuron.

neu·ro·neph·ric (noor"o-nef'rik) pertaining to the innervation of the kidneys.

neu·ro·ne·vus (noor"o-ne'vəs) [*neuro-* + *nevus*] an intradermal nevus in which the nevus cells differentiate into neural-like structures, and may clinically resemble neurofibroma or may have the clinical aspect of a giant hairy pigmented nevus. Called also *neural* or *neuroid nevus*.

neu·ro·ni·tis (noor"o-ni'tis) 1. inflammation of one or more neurons. 2. former name for acute idiopathic polyneuritis.
vestibular n., a disturbance of vestibular function consisting of a single attack of severe vertigo, usually accompanied by nausea and vomiting but without auditory symptoms; it attacks mainly young to middle-aged adults and usually improves within a few days. Called also *endemic paralytic vertigo, epidemic vertigo, paralytic vertigo,* and *vestibular neuritis*.

neu·ro·nop·a·thy (noor"on-op'ə-the) polyneuropathy involving destruction of the cell bodies of neurons.

neu·rono·phage (nōō-ron'o-fāj) [*neuron* + *-phage*] a phagocyte which destroys nerve cells.

neu·rono·pha·gia (noor"on-o-fa'jə) the destruction of nerve cells by phagocytic action.

neu·rono·trop·ic (noor"on-o-trop'ik) [*neuron* + *-tropic*] having a special affinity for neurons.

Neu·ron·tin (nōō-ron'tin) trademark for a preparation of gabapentin.

neu·ro·on·col·o·gy (noor"o-on-kol'ə-je) the field of specialization dealing with tumors of the nervous system.

neu·ro·oph·thal·mol·o·gy (noor"o-of"thəl-mol'ə-je) [*neuro-* + *ophthalmology*] the field of specialization dealing with portions of the nervous system related to the eye.

neu·ro·otol·o·gy (noor"o-o-tol'ə-je) that part of otology dealing especially with portions of the nervous system related to the ear.

neu·ro·pace·mak·er (noor"o-pās'māk-ər) an implant device that relieves pain due to nerve injury.

neu·ro·pap·il·li·tis (noor"o-pap"ĭ-li'tis) papillitis, def. 2.

neu·ro·path·ic (noor"o-path'ik) pertaining to or characterized by neuropathy.

neu·ro·patho·gen·e·sis (noor"o-path"o-jen'ə-sis) development of disease of the nervous system.

neu·ro·patho·ge·nic·i·ty (noor"o-path"o-jə-nis'ĭ-te) the quality of producing or the ability to produce pathologic changes in nerve tissue.

neu·ro·pa·thol·o·gy (noor"o-pə-thol'ə-je) the branch of medicine dealing with morphological and other aspects of disease of the nervous system.

neu·rop·a·thy (nōō-rop'ə-the) [*neuro-* + *-pathy*] a functional disturbance or pathological change in the peripheral nervous system, sometimes limited to noninflammatory lesions as opposed to those of neuritis; the etiology may be known or unknown. Known etiologies include complications of other diseases (e.g., *diabetic n., amyloid n., porphyric n.*) or of toxic states (e.g., *arsenic n., isoniazid n., lead n., nitrofurantoin n.*). Neuropathies affecting a specific may be named for the nerve (e.g., *femoral n.*). The terms *mon ropathy* and *polyneuropathy* may be used to denote whether nerve or several are involved. *Encephalopathy* and *myelopath* corresponding terms referring to the brain and spinal cord, re tively.
acrodystrophic n., hereditary sensory radicular n.
alcoholic n., neuropathy due to thiamine deficiency in chron coholism.
amyloid n., see under *polyneuropathy*.
angiopathic n., neuropathy caused by arteritis of the blood ve supplying the nerves. It is usually a systemic complication of eases such as Wegener's granulomatosis, temporal arteritis, temic lupus erythematosus, rheumatoid arthritis, systemic sc derma, and polyarteritis nodosa; occasional nonsystemic c occur in the form of a mononeuropathy that is more indolent the systemic forms.
arsenic n., arsenical n., see under *polyneuropathy*.
ascending n., that which progresses from the feet upwards to the thigh, hip, trunk, etc.
autonomic n., any neuropathy of the autonomic nervous syst causing symptoms such as orthostatic hypotension, disorde bowel, bladder, or sexual functions, or abnormal pupillary reflex it is a complication of many diseases including Adie's syndro chronic alcoholism, diabetes mellitus, dysautonomia, and Shy-D ger syndrome.
axonal n., axonopathy.
brachial plexus n., brachial plexopathy.
compression n., entrapment n.
Dejerine-Sottas n., progressive hypertrophic n.
Denny-Brown's sensory n., Denny-Brown's sensory radicular hereditary sensory radicular n.
descending n., that which starts proximally (shoulder, hip) spreads distally toward the limb extremities (hands, feet).
diabetic n., any of several clinical types of peripheral neuropa occurring with diabetes mellitus; there are sensory, motor, a nomic, and mixed varieties. The most common kind is a chro symmetrical sensory polyneuropathy affecting first the nerves the lower limbs and often affecting autonomic nerves; pathol cally, there is a segmental demyelination of the peripheral nerv An uncommon acute form is the ischemic variety, accompanied severe pain, weakness, and wasting of proximal and distal musc peripheral sensory impairment, and loss of tendon reflexes. autonomic involvement there may be orthostatic hypotension, turnal diarrhea, retention of urine, impotence, and small diam of the pupils with sluggish reaction to light.
entrapment n., any of a group of neuropathies in which a periphe nerve is injured by compression in its course through a fibrou osseofibrous tunnel or at a point where it abruptly changes course through deep fascia over a fibrous or muscular band. amples include *carpal tunnel syndrome, cubital tunnel syndrome, algia paresthetica, Morton's neuralgia, musculospiral paralysis, nator syndrome,* and *tarsal tunnel syndrome*. Called also *compression syndrome, compression n.*, and *pressure n.*
femoral n., neuropathy due to injury to the femoral nerve, cha terized by a variety of sensory and motor deficits in the leg most common causes are diabetes mellitus, anticoagulant-indu retroperitoneal hemorrhage, and trauma during surgery.
giant axonal n., an autosomal recessive neuropathy of childho characterized by enlarged axons made up of masses of tightly ven neurofilaments.
hepatic n., neuropathy caused by liver disease, particularly o three varieties: an asymptomatic or mild demyelinating poly ropathy, often seen with chronic liver failure; a polyneuritis sim to acute idiopathic polyneuritis, sometimes seen with viral he tis; and a painful sensory neuropathy, sometimes seen with bi cirrhosis.
hypertrophic n., hereditary, progressive hypertrophic n.
hypertrophic n., progressive, a condition characterized by hy plasia of the interstitial connective tissue, causing thickening o ripheral nerve trunks and posterior roots, and by sclerosis o posterior columns of the spinal cord. It is a slowly progressiv milial disease beginning in early life, marked by atrophy of parts of the legs, and by diminution of tendon reflexes an sensation. Called also *Dejerine's disease, Dejerine-Sottas dis disease,* or *n., Gombault's degeneration* or *neuritis, interstitial hy trophic neuritis, hereditary hypertrophic n.*, and *hypertrophic int tial n.* See also *hereditary motor and sensory n.*
hypertrophic interstitial n., progressive hypertrophic n.
ischemic n., an injury to a peripheral nerve caused by a reduc in blood supply, such as that seen with diabetes mellitus.
isoniazid n., polyneuropathy seen in some patients on isoni therapy, consisting of symmetrical numbness and paresthesia the lower extremities.
lead n., a form of segmental (demyelination) neuropathy seen chronic lead poisoning; see under *poisoning*.
Leber's hereditary optic n., Leber's optic n., a rare hereditary

r, resulting from a deficit of ATP caused by mutation of a mi-ondrial gene involved in ATP manufacture and occurring most monly in males, with onset usually at about age twenty; it is acterized by degeneration of the optic nerve and papillo-ilar bundle, resulting in a progressive loss of central vision that remit spontaneously. Called also *hereditary optic n.* or *atrophy, r's optic atrophy,* and *Leber's disease.*

ar plexus n., lumbar plexopathy.

osacral plexus n., lumbosacral plexopathy.

r n., neuropathy or polyneuropathy involving only motor es.

r and sensory n., hereditary (HMSN), any of a group of hered-polyneuropathies involving muscle weakness, atrophy, sen-deficits, and vasomotor changes in the lower limbs. Some dis- in this group have been numbered: types I and II are varieties arcot-Marie-Tooth disease and type III is progressive hyper-ic neuropathy. Called also *hereditary sensory and motor n.*

ple n., 1. polyneuropathy. 2. mononeuropathy multiplex.

furantoin n., neuropathy seen in some patients being treated itrofurantoin; it consists of symmetrical pain and paresthesias feet, which may in time spread to the hands.

tional n., see under *polyneuropathy.*

n., hereditary, Leber's hereditary optic n.

neoplastic n., see under *polyneuropathy.*

xial n., segmental (demyelination) n.

heral n., polyneuropathy.

syric n., see under *polyneuropathy.*

ure n., entrapment n.

l plexus n., sacral plexopathy.

id n., a polyneuropathy sometimes occurring in sarcoidosis, cterized by either cranial polyneuritis or spinal nerve deficits; may be large areas of sensory loss on the trunk.

ental (demyelination) n., neuropathy in which there is loss of n segments; called also *periaxial* or *segmental neuritis* and *dial n.*

n., mild neuropathy occurring in the elderly, affecting chiefly erves of the extremities.

rimotor n., neuropathy or polyneuropathy involving both sen-nd motor nerves.

ry n., neuropathy or polyneuropathy of sensory nerves.

ry n., hereditary, hereditary sensory radicular n.

ry and autonomic n., hereditary (HSAN), any of several in-d neuropathies that involve slow ascendance of lesions of the ry nerves, resulting in pain, distal trophic ulcers, and a variety onomic disturbances. Some diseases in this group have been ered: type I is the autosomal dominant form of hereditary sen-adicular neuropathy; type II is the autosomal recessive form editary sensory radicular neuropathy; and type III is familial tonomia.

ry and motor n., hereditary, hereditary motor and sensory n.

ry radicular n., hereditary, a hereditary polyneuropathy terized by signs of radicular sensory loss in both the upper wer extremities; shooting pains; chronic, indolent, trophic ul-on of the feet; and sometimes deafness. The pathologic find-re primary degeneration of the dorsal root ganglia together vidence of degeneration of the olivary nuclei, optic nerves, rebellum. Most cases are autosomal dominant but a few au-al recessive examples have been reported. The dominant s also called *hereditary sensory and autonomic n. (type I)* and cessive form is also called *hereditary sensory and autonomic e II).* Called also *acrodystrophic n., hereditary sensory n., Denny-'s sensory n.* or *syndrome,* and *ulcerative mutilating acropathy.*

n., serum sickness n., a neurologic disorder, usually involv-cervical nerves or brachial plexus, occurring two to eight fter the injection of foreign protein, e.g., an antiserum or an- of animal origin, and characterized by local pain followed by y disturbances and paralysis. Called also *serum neuritis.*

capular n., a type of entrapment neuropathy caused by a of the suprascapular nerve at the scapular notch, character- pain and weakness at the shoulder joint upon external ro- of the upper arm.

ilous n., an autosomal dominant form of neuropathy char-ed by pain, weakness, and pressure palsy in the arms and myelin sheaths become swollen and sausage-shaped but s neither demyelination nor damage to axons.

- neuropathy caused by ingestion of a toxin; substances com- implicated are *n*-hexane solvents, organophosphorus insec- acrylamide, heavy metals, and a variety of drugs.

tic n., neuropathy resulting from trauma.

tic n., angiopathic n.

ep·tide (noor″o-pep′tīd) any of several types of mole-ound in brain tissue, composed of short chains of amino ac- y include endorphins, enkephalins, vasopressin, and others. e often localized in axon terminals at synapses and are clas- s putative neurotransmitters, although some are also hor-

n. Y, a 36-amino acid peptide found in neurons supplying blood vessels, as well as in the basal ganglia, thalamus, hypothalamus, and dorsal horn of the spinal cord; it is a vasoconstrictor and is believed to play a role in regulation of feeding behavior.

neu·ro·phar·ma·co·log·i·cal (noor″o-fahr″mə-ko-loj′ĭ-kəl) pertaining to neuropharmacology.

neu·ro·phar·ma·col·o·gy (noor″o-fahr″mə-kol′ə-je) [MeSH: Neuropharmacology] that branch of pharmacology dealing especially with the action of drugs upon various parts and elements of the nervous system.

neu·ro·phil·ic (noor″o-fil′ik) neurotropic.

neu·roph·thal·mol·o·gy (noor″of-thəl-mol′ə-je) neuro-ophthalmology.

neu·ro·phy·sin (noor″o-fi′sin) any of a group of soluble proteins (molecular weights 9500–10,500) derived from the precursors of vasopressin, oxytocin, and related hormones, secreted in the hypothalamus. They serve as binding proteins (carrier proteins) for vasopressin and oxytocin and may contribute to hormone storage and transport.

neu·ro·phys·i·ol·o·gy (noor″o-fiz″e-ol′ə-je) [*neuro-* + *physiology*] [MeSH: Neurophysiology] the physiology of the nervous system.

neu·ro·pil (noor′o-pil) [*neuro-* + Gr. *pilos* felt] a dense feltwork of interwoven cytoplasmic processes of nerve cells (dendrites and axons) and of neuroglial cells in the gray matter of the central nervous system.

neu·ro·pile (noor′o-pīl) neuropil.

neu·ro·plasm (noor′o-plaz-əm) [*neuro-* + *-plasm*] the undifferentiated basophilic protoplasm of a nerve cell.

neu·ro·plas·mic (noor″o-plaz′mik) of or relating to neuroplasm.

neu·ro·plas·ty (noor′o-plas″te) [*neuro-* + *-plasty*] plastic surgery of a nerve.

neu·ro·plex·us (noor″o-plek′səs) a plexus of nerves.

neu·ro·po·di·on (noor″o-po′de-on) bouton terminal.

neu·ro·po·di·um (noor″o-po′de-əm) pl. *neuropo'dia* [*neuro-* + *podium*] bouton terminal.

neu·ro·pore (noor′o-por) [*neuro-* + *pore*] the open anterior end (foramen anterius) or the open posterior end (foramen posterius) of the neural tube of the early embryo. These openings gradually close during the fourth week as the primordial spinal cord develops.
anterior n., the embryonic opening in the anterior (or rostral) portion of the forebrain, which closes at the 20-somite stage (about 25 days).
caudal n., posterior n.
posterior n., the embryonic opening at the posterior (or caudal) end of the neural tube, which closes by about the 25-somite stage (about 27 days).
rostral n., anterior n.

neu·ro·pro·ba·sia (noor″o-pro-ba′zhə) [*neuro-* + Gr. *pro* forward + *basis* walking] advance along the nerves; said of the action of certain viruses.

neu·ro·pro·tec·tion (noor″o-prə-tek′shən) protection against neurotoxicity.

neu·ro·pro·tec·tive (noor″o-prə-tek′tiv) guarding or protecting against neurotoxicity.

neu·ro·psy·chi·a·trist (noor″o-si-ki′ə-trist) a physician who specializes in neuropsychiatry.

neu·ro·psy·chi·a·try (noor″o-si-ki′ə-tre) [*neuro-* + *psychiatry*] the branch of medicine which includes both neurology and psychiatry.

neu·ro·psy·cho·log·i·cal (noor″o-si″ko-loj′ĭ-kəl) pertaining to neuropsychology.

neu·ro·psy·chol·o·gy (noor″o-si-kol′ə-je) [*neuro-* + *psychology*] [MeSH: Neuropsychology] a discipline combining neurology and psychology to study the relationship between the functioning of the brain and cognitive processes or behavior, using psychological testing and assessment to assay central nervous system function and diagnose specific behavioral or cognitive deficits or disorders.

neu·ro·psy·cho·met·ric (noor″o-si″ko-met′rik) pertaining to the quantitative testing of neurological processes underlying cognitive processes and behaviors.

neu·ro·psy·cho·phar·ma·col·o·gy (noor″o-si″ko-fahr″mə-kol′ə-je) psychopharmacology.

neu·ro·ra·di·ol·o·gy (noor″o-ra″de-ol′ə-je) radiology of the nervous system.

neu·ro·ret·i·ni·tis (noor″o-ret″ĭ-ni′tis) inflammation of the optic nerve and retina.

neu·ro·ret·i·nop·a·thy (noor″o-ret″ĭ-nop′ə-the) [*neuro-* + *retina* + *-pathy*] a disease of the optic disk and retina.

PQR

par·al·ge·sia (par″əl-je′zē-ə) [*para-* + *algesi-* + *-ia*] any condition marked by abnormal and painful sensations; a painful paresthesia.

par·al·ges·ic (par″əl-je′sik) pertaining to or affected with paralgesia.

par·al·gia (par-al′jə) paralgesia.

para·li·nin (par″ə-li′nin) [*para-* + *linin*] karyolymph.

par·al·lac·tic (par″ə-lak′tik) pertaining to parallax.

par·al·lag·ma (par″ə-lag′mə) [Gr.] displacement of a bone or of the fragments of a broken bone.

par·al·lax (par′ə-laks) [Gr. "change of position"] an apparent displacement of an object due to a change in the observer's position.
binocular p., the seeming difference in position of an object as seen separately by one eye and then by the other, the head remaining stationary. Types include *crossed, direct,* and *vertical p.*
crossed p., binocular parallax occurring in exophoria; when one eye is covered, the object viewed seems to move away from the open eye and toward the covered eye.
direct p., binocular parallax occurring in esophoria; when one eye is covered, the object viewed seems to move toward the open eye and away from the covered eye.
heteronymous p., crossed p.
homonymous p., direct p.
stereoscopic p., binocular p.
uncrossed p., direct p.
vertical p., binocular parallax occurring in vertical diplopia or heterophoria; the object seen seems to move vertically when each eye is closed in turn.

par·al·lel (par′ə-lel) [L. *parallelus*] 1. pertaining to straight lines or planes that do not intersect. 2. pertaining to electric circuit components connected "in parallel" so that the current flow divides, each branch passing through one component, and rejoins; applied by extension to any similar parallel circuit, e.g., the systemic circulation to the various organs. Cf. *series.*

par·al·lel·om·e·ter (par″ə-ləl-om′ə-tər) [*parallel* + *-meter*] an instrument for determining the exact parallel relationships of lines, surfaces, and structures in dental prostheses and casts.

par·al·ler·gic (par″ə-ler′jik) pertaining to or marked by parallergy.

par·al·ler·gy (par-al′ər-je) a condition in which an allergic state, produced by specific sensitization, predisposes the body to react to other allergens with clinical manifestations that differ from the original reaction.

para·lo·gia (par″ə-lo′jə) [*para-* + *log-* + *-ia*] disturbance of the reasoning faculty; marked by delusional or illogical speech.
thematic p., that limited to one subject, on which the mind dwells insistently. Cf. *monomania.*

pa·ral·o·gism (pə-ral′o-jiz-əm) the use of fallacious, meaningless, or illogical thought or language, primarily characteristic of schizophrenia.

pa·ral·o·gy (pə-ral′ə-je) anatomical similarity that has no phylogenetic or functional implication.

pa·ral·y·ses (pə-ral′ĭ-sēz) [MeSH: Paralysis] plural of *paralysis.*

pa·ral·y·sis (pə-ral′ĭ-sis) pl. *paral′yses* [*para-* + *-lysis*] [MeSH: Paralysis] loss or impairment of motor function in a part due to lesion of the neural or muscular mechanism; also, by analogy, impairment of sensory function (sensory paralysis). See also subentries under *hemiplegia, palsy,* and *paraplegia.*

Paralysis

abducens p., paralysis of the external rectus muscle of the eye e to lesion of the abducens nerve, with internal strabismus and plopia.
p. of accommodation, paralysis of the ciliary muscles so as to pre- nt accommodation of the eye.
acute ascending spinal p., acute idiopathic polyneuritis.
p. a'gitans, parkinsonism of unknown etiology, usually occurring in e life, although a juvenile form has been described. It is a slowly ogressive disease characterized by masklike facies, resting tremor, wing of voluntary movements, festinating gait, peculiar posture, d muscle weakness, sometimes with excessive sweating and feel- p of heat. Pathologically, there is degeneration within the nuclear sses of the extrapyramidal system and loss of melanin-containing ls from the substantia nigra and a corresponding reduction in do- mine levels in the corpus striatum. Called also *Parkinson's disease* d *shaking palsy.*
alternate p., alternating p., alternate hemiplegia.
ambiguo-accessorius p., Schmidt's syndrome (def. 1).
ambiguo-accessorius-hypoglossal p., Jackson's syndrome.
ambiguohypoglossal p., Tapia's syndrome.
ambiguospinothalamic p., Avellis' syndrome.
arsenical p., paralysis due to arsenic poisoning.
ascending p., spinal paralysis that progresses cephalad.
Avellis' p., see under *syndrome.*
Bell's p., see under *palsy.*
bilateral p., diplegia; paralysis on both sides.
birth p., paralysis due to injury received at birth.
brachial p., brachial plexus p., paralysis of an arm from lesion of brachial plexus; subdivided into *lower* and *upper brachial plexus alysis* depending on which trunk of the plexus is affected.
brachial plexus p., lower, atrophic paralysis of the muscles of the and hand due to lesions of the eighth cervical or first dorsal nerve er trunk of the brachial plexus). When due to birth trauma it is ed *Klumpke-Dejerine p.*
brachial plexus p., upper, paralysis of arm muscles due to destruc- of the fifth and sixth cervical roots (upper trunk of the brachial us); small hand muscles are unaffected. When due to birth trauma called *Erb-Duchenne p.*
brachiofacial p., paralysis affecting the face and an arm.
Brown-Séquard's p., 1. see under *syndrome.* 2. a flaccid paralysis s in disorders of the urinary tract.
bulbar p., progressive bulbar palsy.
cage p., a complex nutritional deficiency resembling osteomalacia, etimes seen in captive primates.

centrocapsular p., that which is due to lesions of the internal capsule.
cerebral p., any paralysis due to an intracranial lesion; see *cerebral palsy,* under *palsy.*
Chastek p., progressive ataxia and paralysis in silver foxes due to thiamine deficiency following a dietary change from meat to raw fish that contains a thiamine-destroying enzyme.
compression p., paralysis such as crutch paralysis or decubitus paralysis that is caused by pressure on a nerve. Called also *pressure p.*
congenital abducens-facial p., congenital oculofacial p., Möbius syndrome.
conjugate p., loss of ability to perform some of the parallel ocular movements.
coonhound p., acute polyradiculoneuritis.
crossed p., cruciate p., paralysis affecting one side of the face and the opposite side of the body. See also *alternate hemiplegia.*
crural p., that which chiefly affects the thigh or thighs.
crutch p., compression paralysis of one or both arms, due to pressure of the crutch in the axilla.
Cruveilhier's p., spinal muscular atrophy.
curled toe p., a sign of riboflavin deficiency in young chickens; the toes show varying degrees of flexing so that the chick has difficulty walking. Severe deficiency is lethal.
decubitus p., paralysis due to pressure on a nerve from lying for a long time in one position.
Dejerine-Klumpke p., Klumpke's p.
diaphragmatic p., paralysis of the diaphragm, usually unilaterally; called also *phrenoplegia.*
diphtheric p., diphtheritic p., a partial paralysis that often follows diphtheria, chiefly affecting the soft palate and throat muscles. Called also *postdiphtheritic p.*
divers' p., decompression sickness.
Duchenne's p., 1. progressive bulbar palsy. 2. Erb-Duchenne p.
Duchenne-Erb p., Erb-Duchenne p.
Erb's p., 1. Erb-Duchenne p. 2. Erb's spastic paraplegia.
Erb-Duchenne p., upper brachial paralysis, caused by birth injury; called also *Erb's* or *Erb-Duchenne palsy; Duchenne's, Duchenne-Erb,* or *Erb's p.;* and *Duchenne-Erb syndrome.*
facial p., weakening or paralysis of the facial nerve, as in Bell's palsy or Millard-Gubler syndrome.
false p., pseudoparalysis.
Felton's p., see under *phenomenon.*
flaccid p., any paralysis accompanied by loss of muscle tone and absence of tendon reflexes in the paralyzed part. Cf. *spastic p.*

Protective Effects of Flunarizine on Ischemic Injury in the Rat Retina

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• **Intracellular calcium overload has been implicated to be a major factor in triggering cell death after ischemic neuronal injury. We investigated the effects of flunarizine hydrochloride, a calcium-overload blocker, on pressure-induced retinal ischemia in a rat model. Retinal ischemia was induced in albino Lewis rats by increasing the intraocular pressure to 110 mm Hg for 45 minutes. Two regimens of treatment with flunarizine were examined: (1) prophylactic treatment, in which flunarizine was administered before ischemia and in the early phase of reperfusion; and (2) postischemic treatment, in which flunarizine was administered only in the early phase of reperfusion. Injury was evaluated morphologically and morphometrically by measuring the thickness of the inner retinal layers on plastic-embedded retinal sections and by counting the retinal ganglion cells on retinal flat preparations. By morphologic and morphometric criteria, a significant but partial protection of the inner retinal layers was noted in the groups given either regimen. This protective effect of flunarizine suggests that elevated intracellular calcium concentration may play an important role in ischemic retinal injury.**

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The decrease or cessation of blood flow to the central nervous system (CNS) results in focal or diffuse ischemic changes in the neuronal cells. Biochemical, pathophysiologic, and pharmacologic studies of the events that precede ischemia-related cell death have suggested that free radicals, excitatory (cytotoxic) amino acids, intracellular calcium, and cytoplasmic energy supplies are involved in the pathologic processes.[1] Among these factors, an overload of intracellular calcium is postulated to play a central role.[1-3] The imbalance of calcium homeostasis preceding cell death in neuronal cells may occur by a combination of mechanisms: (1) a decrease of Ca^{2+} efflux; (2) an excessive influx of Ca^{2+} through activated voltage-gated or receptor-gated calcium channels; and (3) a release of Ca^{2+} from intracellular stores.[1-3] In the CNS, the modulation of ischemic neuronal injury by different calcium antagonists has suggested that voltage-gated or receptor-gated calcium channels and the release of calcium from intracellular stores may be involved in elevating levels of intracellular calcium.[1-3]

In the retina, which is an integral part of the CNS, the ischemic degenerative changes that are seen in the inner retinal layers have been investigated in many experimental models.[4-8] Recently, such agents as dextromethorphan,[9] MK-801[10] (*N*-methyl-D-aspartate [NMDA] receptor antagonist), nifedipine[11] (calcium blocker), superoxide dismutase (free-radical scavenger),[12] and allopurinol (xanthine oxidase inhibitor),[13] which have been shown to be effective in modulating CNS ischemic injuries, have also been demonstrated to be effective in protecting against ischemic retinal injury. These studies suggested a possible parallelism in the pathologic process of CNS and ischemic retinal injury.

Flunarizine hydrochloride is a class IV calcium overload blocker that has been previously shown to ameliorate ischemic neuronal injury in the brain.[14-25] Its mechanisms of action probably involve the inhibition of voltage-gated or receptor-gated calcium channels[16] and/or inhibition of intracellular calcium release.[25] Since the elevation of intracellular calcium concentration has been proposed to have a major role in neuronal cell death, including retinal neurons, we hypothesized that flunarizine, which readily crosses the blood-brain barrier[26] as well as the blood-retinal barrier,[27] may also ameliorate ischemic retinal injury.

Various experimental models of retinal ischemia have been reported in the literature.[4-13] However, detailed morphologic and morphometric studies to quantitate the various aspects of ischemic retinal injury at different periods after initial drug therapy are lacking. In this report, we used a recently established model of pressure-induced retinal ischemia in the rat[28] to study the effect of flunarizine, and we present a detailed morphologic and morphometric study demonstrating the effectiveness of flunarizine in ameliorating ischemic retinal injury in our rat model.

MATERIALS AND METHODS

Induction of Retinal Ischemia

Adult male albino Lewis rats (Harlan, Indianapolis, Ind), 50 to 60 days old, were anesthetized with intraperitoneal injections of chloral hydrate (400 mg/kg). After topical instillation of 0.5% proparacaine hydrochloride, the anterior chamber of an animal was cannulated with a 26-gauge infusion needle connected to a normal saline (0.9% sodium chloride) container through Silastic tubing (Dow-Corning, Midland, Mich). The intraocular pressure in the cannulated eyes was raised to 110 mm Hg for 45 minutes by elevating the saline container. Retinal ischemia was evident by the whitening of the anterior segment of the eye and blanching of the retinal arteries by fundus examination. At the end of the 45-minute ischemic period, the needle was removed from the anterior chamber, and reperfusion of the retinal vasculature was confirmed by fundus examination. Gentamicin sulfate ointment was applied in the conjunctival sac at the end of the experiment. All animals were treated in accordance with the Association for Research in Vision Sciences and Ophthalmology Resolution on the Use of Animals in Research.

Prophylactic Treatment With Flunarizine

Three groups of rats (six animals in the first two groups and 12 in the third group) were used to evaluate the efficacy of flunarizine given prophylactically. Retinal ischemia was induced bilaterally in the first two groups. The first group (flunarizine-treated group) was treated with three intraperitoneal injections of flunarizine hydrochloride (40 mg/kg, Sigma Chemical Co, St Louis, Mo). The second group (vehicle-treated group) received intraperitoneal injections of the same volume of drug vehicle (40% polyethylene glycol 400 in normal saline, Sigma Chemical Co). The third group did not receive any injection and was divided into two control groups; retinal ischemia was induced unilaterally and the ischemic eyes served as the untreated ischemic control group, while the contralateral eyes without ischemia served as the normal control group.

Injections of flunarizine hydrochloride (4 mg/mL) or the drug vehicle were given 12 hours before the induction of ischemia, immediately after reperfusion (13 hours after the first injection), and 12 hours after reperfusion (25 hours after the first injection). The dosage and schedule of administration of flu-

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